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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/441,443	05/15/95	HOUGHTON M	0063.024

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EXAMINER	
ZEMAN, M	
ART UNIT	**PAPER NUMBER**
1631	24

DATE MAILED: 02/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/441,443	HOUGHTON ET AL.	
	Examiner	Art Unit	
	Mary Zeman	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-48 and 52-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-48,52-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Claims 40-48 and 52-59 are pending in this application.

Applicant's arguments and request for reconsideration filed 11/9/00 have been fully considered but they are not persuasive. Any non-reiterated rejections have been withdrawn.

Claims 40-48 and 52, 56-59 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial asserted utility or a well established utility for the reasons set forth in the previous office action.

Applicant is directed to the Utility Examination Guidelines, Federal Register Vol 66, No 4, Pages 1092-1099, 05 January 2001.

As set forth previously, the specification discloses no credible, specific and substantial utility for any one of the claimed polynucleotides, as defined by the published Utility Examination Guidelines as referred to above.

Applicant argues that utility as an antisense molecule is a well-established utility, evidenced by much later published documents. As set forth in the Guidelines, "the Applicant cannot rebut the rejection by relying on a utility that would not have been readily apparent at the time the application was filed. See, e.g., In re Wright, 999 F.2d 1557, 1562-63, 27 USPQ2d 1510, 1514 (Fed Cir. 1993) ("developments occurring after the filing date of an application are of no significance regarding what one skilled in the art believed as of the filing date.") As such these arguments "confirming the assertions in the specification" are not persuasive.

This application has direct priority to 12/21/1989, and may have priority back to 11/18/1987, the filing date of the earliest parent application. The previous Office Action established that even 10 years after the earliest filing date of the application, antisense molecules of the HCV genome were not a credible, well established utility. (Branch 1998 TIBS Vol 23 pp 45-50) Branch discusses the inoperability of most antisense oligonucleotides *in vitro* and *in vivo*, and the inability to predict what sequences would be useful as antisense molecules. While Applicant has defined various oligonucleotide sequences, the specification fails to support their asserted utility as antisense molecules. The specification does not set forth any teaching of an antisense molecule preventing replication in any system, nor does the art recognize that those oligonucleotides would be expected to be useful as antisense molecules. One of skill in the art of

antisense technology would not have accepted the recited use as being currently available at the time the invention was made, or able to have been used successfully at the time the invention was made for the inhibition of replication of HCV, nor was the technology so well established that one of skill in the art would have been fully versed in how to use the invention at the time the invention was made. As such, further research would have been required to identify or reasonably confirm a "real world" context of use at the time of Applicant's earliest filing. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved would be required. Therefore, the specification does not fairly disclose a substantial utility for the claimed embodiments.

The credibility of an asserted utility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure, and any other evidence of record that is probative of Applicant's assertions. In the absence of such art, and/or other probative evidence (test data, affidavits or declarations from experts in the art, patents or printed publications) from the time the application was filed, this rejection will be maintained. The prior Office Action provides ample reason to doubt the objective truth of the specification's assertions.

Claims 40-48 and 52, 56-59 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 53-55 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 53-55 are drawn to compositions comprising an antisense polynucleotide and an antiviral agent.

Applicant argues that the recitations in the specification are fully enabling for the claimed compositions, and that the publication by Zhang (1999) bears out these teachings. These arguments are not persuasive, for the reasons of record, and those summarized below.

Antisense technology is quite unpredictable, especially in the area of antisense molecules actually having antiviral activity, as evidenced by the art previously cited: (Branch 1998 TIBS Vol 23 pp 45-50.) Branch discusses the inoperability of most antisense oligonucleotides *in vitro* and *in vivo*, and the inability to predict what sequences would be useful as antisense molecules. The prior art does not provide any antisense polynucleotides of HCV which can affect HCV replication, and the skilled artisan could not have predicted those sequences at the time the invention was made. Further, the art does not provide combinations of antisense molecules with other antiviral agents which can affect HCV replication at any stage. The unpredictability of the antisense art, even 10 years after Applicant's earliest filing date, is illustrated by Branch, who reviews the many problems inherent in selecting antisense molecules which will target the intended processes *in vitro* and *in vivo*. Branch even speaks specifically to problems with antisense technology as it relates to HCV at page 48.

Applicant has previously pointed to Section II.H in the specification for support for the claimed invention. The information recited in section II.H does not further illuminate how to choose antisense polynucleotides which would block or prevent protein translation or viral replication, nor does it set forth how to choose other viral agents to be used in combination with any antisense polynucleotide. Section II.H deals with the selection of probes and primers, which would not necessarily perform any antisense functions. The further selection of an antiviral agent to combine with the antiviral is not disclosed, nor are any antiviral agents tested or identified which have any effect on HCV replication.

Applicant has not provided guidance as to what portions of the HCV genome would be useful as antisense polynucleotides, nor what agents would be useful, and how to use this composition. While working examples are not, per se, required, the specification must provide an enabling disclosure for the invention *as it is now claimed*.

The specification, as filed, does not point out oligonucleotides of 8, 10, 12, 15 or 20 nucleotides that would be suitable for use as antisense polynucleotides. There is no direction as to which sequences should be selected from the approximately 9Kb of HCV genome as having antiviral activity. There is no teaching as to which portions of the HCV genome would be susceptible to an antisense blockage, or antiviral agent activity and therefore a suitable region from which the polynucleotide could be selected, nor is there an indication in the specification as

to what length of oligonucleotide is preferred. There is no recitation of particular sequences of polynucleotides useful in the practice of the invention. It is apparent that the polynucleotides may comprise other, non-HCV sequences, as long as there is a stretch of HCV sequence within, which further broadens the scope of the claims. The very large number of potential polynucleotides covered by the scope of the pending claims is an invitation to experiment with the 9000+ nucleotides of HCV-1 and any other HCV or non-HCV sequence, to find polynucleotides which are capable of acting as antisense polynucleotides in the practice of the invention, then to further experiment with an additional antiviral agent to see if any particular combinations have any antiviral activity *in vitro* and/or *in vivo*. While the skill in the art of virology is high, the technology of antisense and antiviral agents is highly unpredictable, in view of Branch, which was published 10 years after Applicant's earliest filing date. Given the lack of working examples, the unpredictability of the art, and the significant further research required to obtain useful compositions of the claims, the specification is not enabling for the invention as now claimed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Since the fee set forth in 37 CFR 1.17(r) for a first submission subsequent to a final rejection has been previously paid, applicant, under 37 CFR 1.129(a), is entitled to have a second submission entered and considered on the merits if, prior to abandonment, the second submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a second submission and the appropriate fee of $770 for a

large entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. If a notice of appeal and the appeal fee set forth in 37 CFR 1.17(e) were filed prior to or with the payment of the fee set forth in 37 CFR 1.17(r), the payment of the fee set forth in 37 CFR 1.17(r) by applicant will be construed as a request to dismiss the appeal and to continue prosecution under 37 CFR 1.129(a). In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 7:30 am and 5:00 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703) 308 4028.

The fax number for this Art Unit is (703) 308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center receptionist whose telephone number is (703) 308-0196.

mkz
February 6, 2001

Marianne P. Allen
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